PROTEOMIC APPROACHES TO UNDERSTAND CHIMIOTHERAPY RESISTENCE IN LEUKEMIAS

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Chronic myeloid leukemia (CML) is a malignant clonal disorder characterized by the Philadelphia (Ph) chromosome translocation, which generates the BCR-ABL fusion gene. It expresses an oncoprotein, known as $p210^{BCR-ABL}$, with constitutive tyrosine kinase activity. Imatinib Mesylate (Gleevec®, Novartis), an orally available ABL kinase inhibitor, can induce hematologic and cytogenetic remission in all stages of CML and now has became the first-line therapy for newly diagnosed CML. Unfortunately, resistance to imatinib occurs frequently during accelerate and blast crisis, resulting in patients relapse. Apart from second-generation BCR-ABL inhibitors the identification of novel direct or indirect downstream targets of BCR-ABL could contribute significantly to the development of new treatment strategies and monitoring approaches in CML. Thus, the identification and analysis of proteomic biomakers in the response to imatinib treatment is extremely necessary to patients follow-up. To address this problem we analyzed through a comparative proteomic approach, the modifications in the protein profile of bone marrow cells from Imatinib Mesylate responsive and resistant patients. IM responsive patients analyzed presents major molecular response and complete hematologic and cytogenetic response within 12 months. Imatinib resistant patients analyzed presents lack of cytogenetic and molecular response. The protein extracts, were analyzed through comparative proteomic approach: 2D electrophoresis assay and MS/MS protein identification with MALDI-TOF-TOF instrument (4700 Applied Biosystems). Mass spectrometry protein identification found 209 proteins present in all samples and 35 differentially expressed protein spots between resistant and responsive samples. Among these proteins we identified several tyrosine kinases, proliferation and apoptosis inhibition related proteins and NuMA1 protein, a BCR-ABL target. NuMA1 expression was also validated in patients samples as IM putative treatment biomarker. All these identifications shed new light on the CML biology and also instigate new approaches that could validate and confirm these biomarkers in CML treatment follow-up.

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